## REMARKS

This Amendment is in response to the Office Action, dated July 2, 2008 ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Claims 9 and 16-17 are pending (claims 1-8 and 10-15 having been previously cancelled). Claim 9 has been amended by virtue of the present amendment. No new matter has been added. Allowance and reconsideration of the application in view of Applicants' amendment and the ensuing remarks are respectfully requested.

Claim 9 has been amended to recite that the anti-microtubule agent is capable of disrupting microtubule dynamics and that the mutant γ actin has an amino acid substitution located in sub-domain I of a wild-type γ actin. Support for this amendment may be found throughout the specification; for example, on page 5, lines 28-30; and page 39, lines 5-6.

In the Office Action, the Examiner acknowledged Applicants' election of Group II (readable upon claims 9 and 16-17).

The specification was objected to as failing to provide a sequence identifier for each individual sequence. Specifically, the Examiner found that each of the sequences listed in the Table at page 16; as well as the sequences noted at pages 33, 37 and 38 must be accompanied by a sequence identifier. Accordingly, as shown in the "Amendment to the Specification" section above, the specification has been corrected to include appropriate sequence identifiers. Additionally, filed herewith is a substitute sequence listing in accordance with 37 C.F.R. §1.1825(a) and (b). The substitute sequence listing adds sequences 11-19. These sequences are found in the specification on pages 16, 33, 37, and 38. No new matter is added. Applicants respectfully request withdrawal of this objection.

The specification was also objected to as containing an obvious typographical error. The Examiner noted that at page 37, line 4, the word "in" should be "is."

Accordingly, as shown in the "Amendment to the Specification" section above, the correction has been made. Applicants respectfully request withdrawal of this objection.

Claims 9 and 16-17 were rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. The Examiner found that the specification is enabled for an *in vitro* method for inducing in a cell, resistance to the antimicrotubule agent desoxyepothiolone B or vinblastine, by providing in a cell, a mutant $\gamma$ actin having an amino acid sequence of SEQ. ID. NOs. 6 or 7. However, the Examiner alleged that the specification does not enable a method for inducing in a cell, resistance to *any* antimicrotubule agent by providing in a cell, *any* mutant $\gamma$ actin. Applicants respectfully traverse this rejection.

Applicants respectfully submit that claim 9, as amended, and claims 16-17 that depend thereon are enabled by the specification. It is well-established that the factors in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The court in *Wands* states, "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Id.* at 1404. The factors to be considered include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary to practice the invention.

Applicants submit that these factors are relevant and thus, must be considered for a proper analysis for fulfilling the enablement requirement in accordance with 35 U.S.C. § 112, first paragraph. The factors to be considered are outlined herein, with support provided by the application as filed.

Applicants submit that (1) the breadth of the claims is not unduly broad but instead is fully supported by the instant application. The claims, as amended, are drawn to methods for inducing in a cell a resistance to an anti-microtubule agent capable of disrupting microtubule dynamics comprising the step of providing in a cell, a mutant $\gamma$ actin, wherein the mutant $\gamma$ actin has an amino acid substitution located in sub-domain I of a wild-type $\gamma$ actin. It is believed that sub-domain I is the site of various

actin-binding proteins (*see* page 3, lines 26-38; and page 39, lines 6-7) and thus, the mutation would disrupt the binding abilities and confer the resistance. Applicants submit that claims 16 and 17 provide that either residue 98 or 103 are leucine. As one of ordinary skill in the art will appreciate, both of these amino acid substitutes occur in sub-domain I, which is taught by the specification to be the site of various actin binding proteins (*See* specification at page 3, lines 26-38 and page 39, lines 6-7). Therefore, with the teaching that an amino acid substitution in sub-domain I can confer resistance, one of skill in the art can appreciate that the claimed method is enabled for inducing cell resistance with the aforementioned mutant γ actin.

Applicants submit that (2) the nature of the invention and (3) the state of the prior art are such that it was well known at the time of filing the instant application that actin and microtubule cytoskeletons have distinct roles within the cell but they closely interact, having the ability to regulate each other's function. Anti-microtuble agents bind to β-tubulin, typically disrupting microtubule dynamics leading to mitotic arrest and/or cell death (see page 5, lines 28-32). Thus, one of ordinary skill in the art can reasonably predict that an agent that disrupts the microtubule cytoskeleton within the cell could also have an affect, whether directly or indirectly, on the actin cytoskeleton. Conversely, one of ordinary skill in the art can reasonably predict that an agent that disrupts the actin cytoskeleton within the cell could also have an affect, whether directly or indirectly, on the microtubule cytoskeleton. Thus, the Examiner's reference to Fojo's comments on disruption of the microtubules *in vitro* does not apply to the present application. Consequently, the Examiner's contention that the specification is not enabled for a method for inducing cell resistance to *any* anti-microtubule agent is incorrect.

With respect to Schaefer *et al.*, Applicants note that Schaefer *et al.* suggests that "tubulin targeting agents (TAAs) that target tubulin itself, rather than interfering with micro-tubule dynamics, would seem to be likely to be more toxic than the standard micro-tubulin targeting agents (MTAs)" (see page. 925, first column). Thus, Schaefer *et al.* teaches PPAR-gamma inhibitors as a different class of compounds that would be effective; that is, a TAA, not an MTA, which is contemplated in the present application.

Applicants submit that (4) the relative skill of those in the art is high; (5) the predictability of the art is high; and (6) the amount of direction or guidance presented in the application is high. Applicants have found that particular mutations of the γ actin gene are associated with resistance to cell death induced by vinblastine, desoxyepothilone B and other anti-microtuble agents. Applicants further provide *in vitro* data demonstrating how to confer in a cell resistance to anti-microtubule agents. Applicants submit that upon this finding, the level of predictability to confer in cell resistance to anti-microtubule agents is high. Furthermore, the specification provides direction and guidance to practice the claimed invention. The specification teaches that introducing a mutant γ actin, particularly within sub-domain I, will confer the resistance and teaches how to introduce the mutation (*see e.g.*, page 30).

Additionally, (7) the presence of working examples, including those on pages 28-30 and pages 40-41, as well as examples of how mutated γ actin nucleic acid molecules can be introduced to the cell (*see e.g.*, page 30) provide adequate examples for one of skill in the art to practice the present claims.

Finally, Applicants submit that (8) the quantity of experimentation required to practice the present claims is not undue. "A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404. Applicants respectfully submit that one of skill in the art could fully practice the present claims without undue experimentation and with a reasonable expectation of success. As shown in Verrills *et al.* (THE JOURNAL OF BIOLOGICAL CHEMISTRY, (2004), 278(46):45082-45093) and Verrills *et al.* (JOURNAL OF THE NATIONAL CANCER INSTITUTE, (October 4, 2006), 98(19):1363-1374), both cited by the Examiner in the present Office Action, methods to confer cell resistance to micro-tubule agents on *in vivo* derived samples were accomplished through routine experimentation.

Applicants respectfully remind the Examiner that a claim is enabled so long a person of ordinary skill in the art "could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 f.2d 778, 785 (Fed. Cir. 1988); MPEP §2164.01.

Moreover, "[a]s long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 32 U.S.C. 112 is satisfied" (emphasis added). *In re Fisher*, 427 F.3d 833, 839 (CCPA 1970); MPEP 2164.01(b). While experimentation may be required to practice these methods, and the amount of that experimentation may even be substantial in some instances, but experimentation is permissible and is not a bar to enablement. Even "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir 1988); MPEP §2164.06.

It is recognized in the art that development of any new treatment entails *in vitro* experiments prior to *in vivo* studies. If the *in vitro* results were as unreliable in terms of predicting *in vivo* results as the Examiner suggests, then nothing would proceed from the *in vitro* stage to testing in humans. There can be no question that Applicants' use of an *in vitro* model is entirely appropriate, as such models are both accepted and commonly used in the art to study human neoplastic disease as the *in vitro* model is clinically predictive of the ability to accomplish the method *in vivo* with a similar methodology.

In the instant application, Applicants' invention includes instructions and examples that would allow one of skill in the art to practice the invention without undue experimentation. This is a complex field of art, and a significant amount of testing may be required to develop and finalize any therapeutic medical intervention. However, this issue has been revisited on numerous occasions by the courts, and every time the answer is the same: that even the need for substantial but routine experimentation does not preclude patentability on grounds of enablement.

Accordingly, for all of the aforementioned reasons, Applicants respectfully submit that the pending claims are fully enabled in light of the instant application at the time filing and therefore, this rejection under §112, first paragraph, has been overcome and request that the rejection be withdrawn.

Claims 9 and 16-17 were rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description of the invention. The Examiner contends that the

specification does not convey to one skilled in the art that the inventors had possession of the claimed invention because one skilled in the art allegedly cannot envision all the contemplated γ actin mutant possibilities and because there is no correlation between the structure and activity of inducing resistance to an anti-microtubule agent. Applicants respectfully traverse this rejection.

As discussed *supra*, the claims, as amended, recite that mutant γ actin has an amino acid substitution located in sub-domain I of a wild-type γ actin, which is believed to be the site of various actin-binding proteins. One of skill in the art can envision the contemplated γ actin mutant possibilities because there is a correlation between the structure and activity of inducing resistance to an anti-microtubule agent. The structure of having a mutation within the site of actin-binding proteins to disrupt binding is correlated to the activity of inducing resistance. In light of the foregoing, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Claims 9 and 16-17 were rejected under 35 U.S.C. §102(f) based on the assertion that Applicants did not invent the claimed subject matter. The Examiner cited Po'uha (*Ph.D. Dissertation*, UNIVERSITY OF NEW SOUTH WALES, AUSTRALIA, (2006), 1-256) and asserted that Po'uha describes the subject matter of the invention. The Examiner also cited Verrills (*Ph.D. Dissertation, Mechanisms of Resistance to Anti-microtubule Agents in Childhood Leukemia*, MACQUARIE UNIVERSITY, SYDNEY, NSW, AUSTRALIA) as basis for this §102(f) rejection. Applicants respectfully traverse this rejection.

In regard to the assertion that Dr. Po'uha invented the subject matter as claimed in the present patent application, Applicants respectfully submit that the Examiner is mistaken. While Applicants agree with the Examiner that a Ph.D. candidate must exhibit original and independent research, the candidate must also provide some context and background for that work. This is usually in the form of a "literature review" at the beginning of the dissertation (*e.g.*, Chapter I). While the candidate makes a declaration that the work contained therein is his own, it is accepted that this chapter is written by the candidate but it is not expected that he had necessarily performed the work that is referred to in the papers that are referenced as part of the review. The information disclosed in Fig 1.1 and page 19 of the dissertation that the Examiner

suggested as describing the present invention is information that forms part of the literature review as background to Dr. Po'uha's work resulting in the dissertation submitted in 2006. In the figure description, it is clearly stated that it has been adapted from a previous paper (Verrills, 2004). Both the dissertation and the cited paper were published after the priority date of the present application. Therefore, it not a surprise that this information forms part of Dr. Po'hua's literature review in Chapter I of the dissertation. Additionally, Applicants remind the Examiner that while Verills *et al.* (J Natl Cancer Inst. 2006 Oct 4;98(19)) indicated that Dr. Po'uha contributed equally to the work, the standard in determining authorship for a journal publication is different than that for determining inventorship. In the instant application, Dr. Po'uha is not an inventor as explained above.

With respect that the assertion that Dr. Nicole Verrills invented the subject matter as claimed in the present patent application, Applicants submit that the Examiner may have overlooked the file history. As outlined in the Decision on Request issued by the United States Patent and Trademark Office on January 12, 2007, inventorship was corrected and Dr. Nicole Verrills was added as a co-inventor on the present patent application. As such, Applicants indeed invented the claimed subject matter. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §102(f).

//.. p. 12

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
Maria KAVALLARIS *et al.*
DAVIS WRIGHT TREMAINE LLP

By _____
Linda B. Truong, Esq.
Registration No. 56,461

865 South Figueroa Street, Suite 2400
Los Angeles, CA 90017-2566
Phone: (213) 633-6800
Facsimile: (213) 633-6899